

PATENT COOPERATION T<sup>Y</sup>

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark  
Office  
(Box PCT)  
Crystal Plaza 2  
Washington, DC 20231  
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 18 November 1998 (18.11.98)	
International application No. PCT/CA98/00346	Applicant's or agent's file reference CG/11957.34
International filing date (day/month/year) 09 April 1998 (09.04.98)	Priority date (day/month/year) 10 April 1997 (10.04.97)
Applicant BUSSEMAKERS, Marion, J., G.	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
04 November 1998 (04.11.98)

☐ in a notice effecting later election filed with the International Bureau on:  
\_\_\_\_\_

2. The election ☒ was  
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Maria Victoria CORTIELLO Telephone No.: (41-22) 338.83.38
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## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>CG/11957.34</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/CA 98/ 00346</b>	International filing date (day/month/year) <b>09/04/1998</b>	(Earliest) Priority Date (day/month/year) <b>10/04/1997</b>
Applicant <b>DIAGNOCURE INC. et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ Certain claims were found unsearchable (see Box I).

2. ☐ Unity of invention is lacking (see Box II).

3. ☒ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing

☐ filed with the international application.

☒ furnished by the applicant separately from the international application,

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ Transcribed by this Authority

4. With regard to the title, ☒ the text is approved as submitted by the applicant

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

Figure No. 1 ☒ as suggested by the applicant.

☐ None of the figures.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 98/00346

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/00 C12N15/12 C12N5/12 C12N1/21 C07K14/47  
C07K16/18 C12Q1/68 G01N33/577 A61K39/395 A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K C12Q G01N A61K A01K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
O, X	BUSSEMAKERS M J G ET AL: "DD3: A new prostate specific marker, overexpressed in prostatic tumors." 87TH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, WASHINGTON, D.C., USA, APRIL 20-24, 1996. PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING 37 (O). 1996. 515. ISSN: 0197-016X, XP002074304	1-8, 12, 13
Y	abstract no. #3522 see abstract --- -/--	9-11, 23



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## ° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance  
"E" earlier document but published on or after the international filing date  
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  
"O" document referring to an oral disclosure, use, exhibition or other means  
"P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.  
"&" document member of the same patent family

Date of the actual completion of the international search

13 August 1998

Date of mailing of the international search report

25/08/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Hornig, H

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 98/00346

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
O,X	BUSSEMAKERS M J G ET AL: "DD3: A new prostate-specific marker, strongly overexpressed in prostatic tumors." 12TH CONGRESS OF THE EUROPEAN SOCIETY FOR UROLOGICAL ONCOLOGY AND ENDOCRINOLOGY, ESSEN, GERMANY, MARCH 6-8, 1997. UROLOGICAL RESEARCH 25 (1). 1997. 76. ISSN: 0300-5623, XP002074305	1-8,12, 13
Y	abstract no. 02.2 see abstract	9-11,23
Y	EP 0 520 794 A (HOFFMANN LA ROCHE ;UNIV CALIFORNIA (US)) 30 December 1992 see the whole document	9,10,23
Y	WO 95 28498 A (UNIV COLUMBIA ;KATZ AARON E (US); BUTTYAN RALPH (US); RAFFO ANTHON) 26 October 1995 see the whole document	9,10,23
Y	WO 94 09820 A (SLOAN KETTERING INST CANCER ;ISRAELI RON S (US); HESTON WARREN D W) 11 May 1994 see the whole document	9,10,23
Y	WO 96 14875 A (UNIV CALIFORNIA) 23 May 1996 see the whole document	11
A	EP 0 160 228 A (CETUS CORP) 6 November 1985	1-23
O,P, X	TAMIMI Y ET AL: "DiagnoGene PCA3 reliable NASBA based reagents for detecting PCA3 mRNA, a recently described prostate marker." 89TH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, NEW ORLEANS, LOUISIANA, USA, MARCH 28-APRIL 1, 1998. PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING 39 (0). 1998. 234. ISSN: 0197-016X, XP002074308 see abstract	1-13,23

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA 98/00346

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Remark: Although claim(s) 21 and 22  
is(are) directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 98/00346

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0520794	A	30-12-1992	AU 662906 B	21-09-1995
			AU 1846592 A	07-01-1993
			CA 2072314 A	27-12-1992
			DE 69223284 D	08-01-1998
			DE 69223284 T	25-06-1998
			DK 520794 T	27-04-1998
			ES 2111047 T	01-03-1998
			JP 5269000 A	19-10-1993
			US 5543296 A	06-08-1996
			US 5766888 A	16-06-1998
WO 9528498	A	26-10-1995	AU 2292495 A	10-11-1995
			CA 2187775 A	26-10-1995
			EP 0760006 A	05-03-1997
WO 9409820	A	11-05-1994	CA 2147499 A	11-05-1994
			EP 0668777 A	30-08-1995
			JP 8506005 T	02-07-1996
			US 5538866 A	23-07-1996
WO 9614875	A	23-05-1996	AU 4148996 A	06-06-1996
			EP 0793508 A	10-09-1997
EP 0160228	A	06-11-1985	US 4690890 A	01-09-1987
			AU 583818 B	11-05-1989
			AU 4084585 A	10-10-1985
			CA 1252388 A	11-04-1989
			DK 155585 A	05-10-1985
			JP 60228962 A	14-11-1985

REC'D 28 JUL 1999

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference CG/12228.4	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/CA98/00346	International filing date (day/month/year) 09/04/1998	Priority date (day/month/year) 10/04/1997
International Patent Classification (IPC) or national classification and IPC C12N15/00		
Applicant DIAGNOCURE INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 8 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  04/11/1998	Date of completion of this report  21.07.99
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer  Meyer, W  Telephone No. (+49-89) 2399 8157 

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA98/00346

## I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

### Description, pages:

1-83 as originally filed

### Claims, No.:

1-23 as originally filed

### Drawings, sheets:

1/8-8/8 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

## IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/CA98/00346

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
- ☒ not complied with for the following reasons:

**see separate sheet**

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
- ☒ all parts.
- ☐ the parts relating to claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes:	Claims	14-22
	No:	Claims	1-13 and 23
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-23
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	21-23 (opinion reserved)

2. Citations and explanations

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/CA98/00346

**Re Item IV**

**Lack of unity of invention**

1. Reference is made to the following documents:  
D1: 87th Annual Meeting of the American Association For Cancer Research, Washington, D.C., USA, April 20-24, 1996.  
D2: Proceedings of the American Association For Cancer Research Annual Meeting 37 (0). 1996. 515  
D3: EP 0 520 794 A 30 December 1992  
D4: 89th Annual Meeting of the American Association For Cancer Research, New Orleans, USA, March 28- April 1, 1998
2. The International Search Report has been drawn up in respect of the entire international application, but the IPEA finds that the application does not comply with the requirement of unity of invention (Article 34(3) and Rule 13 PCT).
3. An international application must relate to one invention only or to a group of inventions so linked as to form a single general inventive concept.  
Unity of invention is fulfilled only when there is a technical relationship between the inventions involving one or more of the same or corresponding special technical features, special technical features being such features, that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.
4. The technical relationship among the independent claims is the provision of a gene designated in the application PCA3, which is related to prostate cancer. However, this relation cannot be accepted to consist of special technical feature as defined above since it does not define a contribution which each of the different claimed inventions, considered as a whole makes over the prior art.  
In fact, the gene PCA3, also named DD3 (see also point 7. below), which is related to prostate cancer has already been disclosed in D1 or D2 (D1 and D2, see entire Documents). Thus, this feature cannot be accepted as a special technical feature as required by Rule 13 PCT.

5. Consequently, the technical relationship of the independent claims does not embrace a special technical feature, within the meaning of Rule 13.2 PCT. The following inventions have to be considered separately:
1. **Claims 1-8 and 11-16** are referring to the nucleic acid molecules and their corresponding amino acids of PCA3
  2. **Claims 9, 10 and 17-23** are referring to the analysis of the presence of the PCA3 gene and its product, to a diagnostic kit and methods of treating and/or diagnosing prostate cancer

**Re Item V**

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

6. As the priority document for the application was not available at the time of drafting of the present written opinion, it is established under the assumption that the entire subject-matter is entitled to the claimed priority. If this is not the case, the 'P' document cited in the search report may have to be considered for novelty and/or inventive step. This document (published by the inventor) would be detrimental to most, if not all, of the claimed subject-matter (Article 33(2), (3) PCT).
7. The subject-matter of **claims 1-8 and 11-13** is not new in the sense of Article 33(2) PCT. The subject-matter is anticipated by D1 which describes the identification of a gene designated DD3 and its initial characterisation (e.g. the transcription unit of DD3 and the genomic mapping). This gene, which is in the application and also in a later published document (see D4) called PCA3 appears to be the same as the claimed one. The additional characterising feature like e.g. the exact sequence is considered to be an inherent feature of the known gene disclosed in D1. Consequently D1 discloses according to present **claims 1-8 and 11-13**, an isolated nucleic acid molecule or a recombinant nucleic acid molecule encoding prostate cancer antigen 3 (PCA3).
8. The subject-matter of **claims 9, 10 and 23** is not new in the sense of Article 33(2) PCT. The subject-matter is anticipated by D2, which discloses according to

present **claims 9, 10 and 23** a method of determining (diagnosing) the presence of development prostate cancer in a patient by determining the amount of DD3 (D2, entire Document). As mentioned above (see point 3.), it appears that DD3 is the same as PCA3. Consequently **claims 9, 10 and 23** do not fulfil the requirement of Article 33(2).

9. **Claims 21 and 22** are dependent on the subject-matter of **claims 1-8 and 11-13**. The subject-matter of these claims do not appear to include any additional matter which would render them inventive as such. They appear to be concerned with mere technical variations of the known subject-matter of **claims 1-8 and 11-13** and do not satisfy the criterion set forth in Article 33(3) PCT:

D2 is considered to represent the closest prior art and discloses the use of a gene designated DD3 (PCA3) in order to diagnose prostate cancer. D2 further discloses the possibility for the treatment of this disease (D2, last paragraph). The difference between D2 and the subject-matter of **claims 21 and 22** of the present application is the inhibition of the expression of DD3 (PCA3). Starting from D1, the underlying technical problem is how to inhibit the expression of DD3 in order to treat prostate cancer.

The subject-matter of the claims referred to above is considered to solve this problem. However, the solution proposed in **claims 21 and 22** of the present application cannot be considered as involving an inventive step (Article 33(3) PCT for the following reasons:

D3 discloses a way to inhibit the expression of another gene related to prostate cancer (D3, Claims 12, 13, 30 and 39). Combining the teachings of D3 with the closest prior art, a skilled person would arrive at the claimed solution to the above problem as set out in **claims 21 and 22** without the need for any inventive effort. Consequently, **claims 21 and 22** do not fulfil the requirements of Article 33(3) PCT.

10. The remaining **claims 14-20** are concerned with matter which can be obtained in an obvious manner. Once a gene is available, claims related to the creation of a transgenic non-human organism (**claim 14**), or the expression and purification of the gene product (**claims 15-16**), or to antibodies and their use (**claims 17-20**) would be a matter of mere routine performance for person skilled in the relevant field. Consequently **claims 14-20** would fulfil the requirements Article 33(3) PCT

only in combination with a novel and inventive main claim.

11. For the assessment of the present **claims 21-23** on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item VIII**

**Certain observations on the international application**

12. **Claims 1-3 and 8-10, 15, 16, 18, 22 and 23** lacks clarity contrary to Article 6 PCT as the internal arbitrary designation "Prostate cancer antigen 3 " and "PCA3" is not a recognized denomination or abbreviation. Such entities should be clearly and unambiguously characterized by reference to technical features such as SEQ ID NO. or by reference to the deposition number, which would unambiguously define the sequence of "Prostate cancer antigen 3 " or "PCA3".
13. The accession numbers as used in **claims 2 and 4** are without an indication of an exact reference point (e.g. SEQ ID NO.) unclear contrary to Article 6 PCT.
14. The expression "specifically hybridise" is vague and not suitable to clearly define the scope of **claim 1**. Without any indication of the reaction condition to be used for hybridisation this is an essentially undefined term which is open to individual interpretation (Article 6 PCT).
15. The expression "exon 1, 2, 3, 4a, 4b, 4c, or 4d" is vague and not suitable to clearly define the scope of **claim 8**. Without any indication of the exact sequence composition this an essentially undefined term which is open to individual interpretation (Article 6 PCT).

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/CA98/00346

16. The subject-matter of **claim 8** should be defined by means of positive features. A disclaimer may be used only when the claim's subject-matter cannot be defined more clearly and concisely by means of positive features (PCT Guidelines III 4.12).
17. **Claims 9, 18, 21 and 22** does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added (i.e. the wording "under conditions such that hybridization occurs" (**claim 9**) or "under conditions such that immunocomplexes form" (**claim 18**) "therapeutically effective amount" (**claims 21 and 22**) merely amounts to the statement of the underlying problem). According to the PCT Guidelines C III 4.7, the area defined by the claims must be as precise as the invention allows. That means that claims which attempts to define the invention, or a feature thereof, by a result to be achieved, should not be allowed.
18. The term "epitope-bearing portion" as used in **claims 15-17** lacks clarity due to the wording. This expression renders the scope of the claims vague and technically unclear, since no exact sequence compositions are given (Article 6 PCT).
19. The term "purified" as used in **claim 16** lacks clarity. This expression renders the scope of the claims unclear, since no indication of the grade of purity is given (Article 6 PCT).
20. The term "specific binding affinity" as used in **claim 17** is vague. A person skilled in the art does not know which exact quantity such a binding should have (Article 6 PCT).
21. It appears that SEQ ID NO. 2 and SEQ ID NO. 7 refer to identical sequences. Consequently, the subject-matter of **claim 2b** and part of **claim 5** (referring to SEQ ID NO. 7) appears to be superfluous (Article 6 PCT).